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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/754,446
Filing Date: January 09, 2004
Appellant(s): SUN ET AL.

Barry S. Wilson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 05/11/2007 appealing from the Office action mailed 10/11/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Edelmann. L. et al "Carrier screening for mucolipidosis type IV in the American Ashkenazi Jewish population" Am J Hum Genet. 2002 Apr;70(4):1023-7.

GenBank AF287270 (2000) "Homo sapiens mucolipin (MCOLN1) gene, complete cds", pages 1-5.

Doll M.A. et al "Rapid genotype method to distinguish frequent and/or functional polymorphisms in human N-acetyltransferase-1" Anal Biochem. 2002 Feb 15;301(2):328-32.

Buck G.A. et al "Design strategies and performance of custom DNA sequencing primers" Biotechniques. 1999 Sep;27(3):528-36.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 19, 23-25, 28, 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edelmann et al (2002) as evidenced by GenBank AF287270 (2000) in view of Doll et al (2002).

The GenBank AF287270 sequence is the source of all nucleotide position numbers referenced in this rejection.

Edelmann et al teaches a method to screen for specific mutations (p.1023, right col., lns.14-20) responsible for causing Mucolipidosis IV. The method comprises steps

of amplifying relevant portions of the MCOLN1 gene with appropriate primers (p.1024, left col., lns.26-47), and detecting the presence of wildtype or mutant gene sequences by hybridization to probes specific probes (p.1024, right col., lns.15-20).

Regarding claim 19, Edelmann et al teaches a method for determining the presence of a 6,434-bp deletion mutation spanning nucleotides 511-6,944 (designated in the reference as '511del6434') in the MCOLN1 gene. The method comprises the steps of contacting a nucleic acid sample with primers for amplification: relevant to step i) of claim 19, the MLIV-3UPS primer (p.1024, left col., lns.32-34) is complementary the 20 nucleotides from position 241 to position 260, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene; relevant to step ii) of claim 19, the MLIV-4UPS primer (p.1024, left col., lns.34-35) is complementary to the 20 nucleotides from position 7017 to 7036, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 6956-7356 of the MCOLN1 gene. Relevant to step iii) of claim 19, Edelmann et al teaches the detection of the mutant sequence using a probe (p.1024, right col., lns.19-20) complementary to nucleotides from positions 503-510 and positions 6944-6954, thus satisfying the limitations of the claim because the probe is complementary to a sequence that is amplified from a template DNA that possesses the 511del6434 using the primers of steps i) and ii).

Regarding claim 25, Edelmann et al teaches the multiplexing of PCR amplification for detecting the presence of one or both of the IVS3-2A→G mutation (p. 1023, right col. lns.14-16) and the 511del6434 mutation (p.1024, left col., lns.12-15; p.1024, left col., ln.47 – p.1024, right col., ln.2; Fig.1; Fig.2). The method comprises the steps of contacting a nucleic acid sample with primers for amplification, and probes for the detection of mutant sequences. Relevant to step i) of claim 25, the MLIV-1UPS primer (p.1024, left col., lns.28-29) is complementary to the 20 nucleotides from position 5361 to position 5380, thus satisfying the requirement that the primer is complementary to a 15-30 bp segment of DNA between positions 5124-5524 of the MCOLN1 gene; relevant to step ii) of claim 25, the MLIV-2UPS primer (p.1024, left col., lns.29-31) is complementary to the 20 nucleotides from position 5711 to position 5730, thus

satisfying the requirement that the primer is complementary to a 15-30 bp segment of DNA between positions 5541-5941 of the MCOLN1 gene. Relevant to step iii) of claim 19, Edelmann et al teaches the detection of the mutant sequence using a probe (p.1024, right col., ln.18) that is complementary to the 19 nucleotides from position 5523 to position 5541, thus satisfying the requirement that the probe is complementary to a segment of DNA that includes position 5534 of the MCOLN1 gene. Relevant to step iv) of claim 19, the MLIV-3UPS primer (p.1024, left col., lns.32-34) is complementary the 20 nucleotides from position 241 to position 260, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene; relevant to step v) of claim 19, the MLIV-4UPS primer (p.1024, left col., lns.34-35) is complementary to the 20 nucleotides from position 7017 to 7036, thus satisfying the limitation of the claim that the primer is complementary to a 15-30 bp segment of DNA between positions 6956-7356 of the MCOLN1 gene. Relevant to step vi) of claim 19, Edelmann et al teaches the detection of the mutant sequence using a probe (p.1024, right col., lns.19-20) complementary to nucleotides from positions 503-510 and positions 6944-6954, thus satisfying the limitations of the claim because the probe is complementary to a sequence that is amplified from a template DNA that possesses the 511del6434 using the primers of steps iv) and v).

Regarding claim 28, Edelmann et al teaches the sequence of the mutant IVS3-2A→G probe (p.1024, right col., ln.18), which is complementary to nucleotide positions 5523-5541of the MCOLN1 gene, thus overlaps and contains the sequence of SEQ ID NO: 6 (which is complementary to nucleotide positions 5526-5540 of the MCOLN1 gene), and thus is comprised of and consists essentially of the claimed sequence.

Regarding claim 34, Edelmann et al teaches the sequence of the 'normal' IVS3-2A→G probe (p.1024, right col., ln.17), which is complementary to nucleotide positions 5523-5541of the MCOLN1 gene, thus overlaps and contains the sequence of SEQ ID NO: 5 (which is complementary to nucleotide positions 5526-5540 of the MCOLN1 gene), and thus is comprised of and consists essentially of the claimed sequence.

Edelmann et al does not teach the detection of specific sequences (the deletion mutation, the single nucleotide mutation, or the wildtype 'normal' sequence) using

probes that are labeled with detectable labels (comprising a donor fluorophore and a quencher moiety), and monitoring the accumulation of amplified nucleic acid in real time by detecting changes in fluorescence.

Doll et al teaches a method to genotype several polymorphic sites within a gene using TaqMan real time PCR analysis and probes labeled with fluorescent reporters.

Relevant to claim 19 (step iii) and part b)), claim 24, claim 25 (steps iii) and vi), and part b)), and claim 33, Doll et al teaches the detection of specific sequences using a real time PCR method in which the fluorescence signal increases when the probe with the exact sequence match binds to the template DNA and is digested by the exonuclease activity of the polymerase, thus releasing the reporter dye from the quencher (p.330, right col., ln.24 – p.331, right col., ln.6; Fig.2).

Relevant to claims 23 and 32, Doll et al specifically teaches the use of the reporter dyes FAM, VIC, and TET (p.330, left col., lns.50-56).

Relevant to claim 34, Doll et al teaches the multiplexed use of the fluorescently labeled reporter probes (p.330, right col., lns.11-24; Table 2; Fig 1) for the detection of different sequences within the same nucleic acid sample.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the mutation detection methods of Edelmann et al to have used the real time PCR detection methods of Doll et al et al. One would have been motivated to do so based on the assertion by Doll et al that the real time PCR based method is a rapid method for the analysis of nucleic acid sequences that is reliable, does not require radioactivity, and is suitable for automated applications (p.331, left col., ln.7 – p.331, right col., ln.11). One would have had a reasonable expectation of success because Doll et al teaches the successful analysis of multiple nucleic acid mutations within a given nucleic acid sample (Fig.2 of Doll et al et al) similar to the analysis of the multiple mutations of the MCOLN1 gene (Fig.2 of Edelmann et al).

Claims 20-22, 26, 27, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edelmann et al (2002) in view of Doll et al (2002), and further in view of GenBank AFAF287270 (2000) and Buck et al (1999).

The teachings of Edelmann et al in view of Doll et al are applied to claims 20-22, 26, 27, and 29-31 as they were previously applied to claims 19, 23-25, 28, 32-34.

Edelmann et al teaches methods for detecting mutations in the MCOLN1 gene using primers and probes that are functionally equivalent (i.e. primers that amplify the relevant mutation-containing portions of the MCOLN1 gene, and probes that detect the particular mutations within the MCOLN1 gene) to the primers and probes required by the claims. Specifically, Edelmann et al teaches: the MLIV-3UPS primer (p.1024, left col., lns.32-34) which has a binding site 180nt upstream of SEQ ID NO: 3 (which hybridizes to nucleotides 441-460); the MLIV-4UPS primer (p.1024, left col., lns.34-35), which overlaps the 20 of the 21 nucleotides in the sequence of SEQ ID NO: 4 (which hybridizes to nucleotides 7037-7017); the 511del6434 probe (p.1024, right col., lns.19-20) for detection of the sequence created by the MCOLN1 deletion mutation which has a binding site 24nt upstream of SEQ ID NO: 7 (which hybridizes to nucleotides 6982-6997); the MLIV-1UPS primer (p.1024, left col., lns.28-29) which has a binding site 50nt upstream of SEQ ID NO: 1 (which hybridizes to nucleotides 5495-5509); and the MLIV-2UPS primer (p.1024, left col., lns.29-31) which has a binding site 10nt downstream of SEQ ID NO: 2 (which hybridizes to nucleotides 5698-5677).

Edelmann et al in view of Doll et al does not teach primers comprised of sequences that consist essentially of SEQ ID NO: 3 (as required by claims 20 and 29), SEQ ID NO: 4 (as required by claims 21 and 30), SEQ ID NO: 1 (as required by claim 26), or SEQ ID NO: 2 (as required by claim 27); or a probe comprised of a sequence that consists essentially SEQ ID NO: 7 (as required by claims 22 and 31).

GenBank AF287270 teaches the complete nucleic acid sequence of the MCOLN1 gene from humans, which includes the positions of the MLIV-4UPS, MLIV-3UPS, MLIV-1UPS, and MLIV-2UPS primers and the 511del6434 probe from Edelmann et al, as well as SEQ ID NOs 1, 2, 3, 4 (paragraphs [0035]-[0036]; Table 1) and SEQ ID NO: 7 (paragraph [0050]; Table 2) from the instant application. Furthermore, Buck et al

expressly provides evidence of the equivalence of primers. Specifically, Buck et al invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al tested each of the primers selected by the methods of the different labs, Buck et al found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Therefore, it would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the detection methods of Edelmann et al in view of Doll et al to use any primers based on the MCOLN1 gene sequence of GenBank AF287270, especially sequences which are in close proximity to those taught by Edelman et al. One would have been motivated to use any appropriate primers within the MCOLN1 sequence based on the assertion of Edelmann et al that MCOLN1 gene mutations are useful for screening for Mucolipidosis Type IV. One would have been motivated to modify the primers taught by Edelmann et al in order to have provided additional primer pairs useful in Mucolipidosis Type IV screening. One would have had a reasonable expectation of success based on the indication of Edelmann et al that amplification and probing methods can be used to detect Mucolipidosis Type IV related mutations in the MCOLN1 gene, and the results of Buck et al that teach the successful use of primers with a wide variety of sequences.

(10) Response to Argument

Appellants have argued that Edelmann et al in view of Doll et al fail to teach or suggest every element of the claimed method (part 1.3 of the Appeal Brief). Appellants argue that Doll et provides a method for detecting single nucleotide polymorphisms, but does not teach or suggest a method for detecting deletion mutations, as required by claim 19. The Examiner maintains that Appellants interpretation of the teachings of Doll et al is too narrow. Doll is relied upon for teaching of methods using primers and probes in the real-time detection of specific nucleotide sequences. Doll is not relied upon for teaching the real-time detection of a particular nucleotide sequence, or the nucleotide sequence instantly claimed. However, Doll et al does teach a specific example of the detection of nucleotide content at the position of a single nucleotide polymorphism, and thus Doll et al provides for a general methodology for the detection of particular nucleotide content. Doll et al does not provide any teaching away from the application of the methods of their methods for the detection of a nucleotide sequence resulting from a deletion mutation within a known nucleotide sequence. The teachings of Edelmann et al is relied upon for teaching the specific nucleotide sequence content resulting from the deletion mutation in the MCLON1 gene that is causative of Mucolipidosis IV. Edelmann et al further provides primers for the PCR-based amplification of, and a probe for the hybridization-based detection of, the specific nucleotide sequence content resulting from the deletion mutation in the MCLON1 gene that is causative of Mucolipidosis IV, where the primers and probes satisfy the broad

limitations of the rejected claims. As such, the Examiner maintains that the combination of Edelmann et al and Doll et al teaches every limitation of the claimed methods.

Appellants argue (part 1.4 of the Appeal Brief) that there is no motivation to combine the teachings of Edelmann et al and Doll et al. Appellants argue that the Examiner has failed to identify a reason why a skilled artisan would be motivated to modify the portion of the method of Edelmann et al which relates to detecting deletion mutations with anything taught by Doll et al which is directed solely to the detection of point mutations. The Examiner maintains that while Doll et al provides a specific example of the detection of nucleotide content at the position of a single nucleotide polymorphism, the teaching of Doll et al is the teaching of methods using primers and probes in the real-time detection of specific nucleotide sequences. Regarding motivation to use the methods of Doll et al, as clearly indicated in the rejection, Doll et al provides explicit motivation for using the methods taught in Doll et al for the detection of specific nucleotide sequence content on p.331, left col., ln.7 – p.331, right col., ln.11 where it is asserted by Doll et al that the real time PCR based method provides major advantages in that it is a rapid method for the analysis of nucleic acid sequences that is reliable, does not require radioactivity, and is suitable for automated applications. Thus Doll et al provides teaching of the general methodology required for the claimed methods and the benefits of the methodology, and the skilled artisan would have realized the benefits and applied the methodology to the examination of other nucleic acid sequences in other analyses. And while the argument indicates that Doll et al and Edelmann et al fail to teach or suggest the use of allele-specific oligonucleotides to

detect deletion mutations, the Examiner maintains, as set forth in the rejections, that Edelmann et al clearly teaches the use of allele-specific oligonucleotides for the detection of deletion mutations.

With regard to the rejection of claims 25, 29, and 32-38, Appellants argue (part 2.1 of the appeal Brief) that Edelmann et al in view of Doll et al fail to teach or suggest every element of the claimed method which requires a multiplex PCR using a primer pair which flanks the deleted region and another primer pair which flanks the site of the point mutation. The Examiner maintains that Edelmann et al, as set forth in the rejection, clearly teaches the multiplex amplification of the deleted region and the point mutation (p.1024, left col., lns.23-36) using primers that satisfy the broad limitations of the rejected claims. Concerning Appellants arguments that Doll et al do not detect any deletion mutations, and as such the methods of Doll et al can not be used to detect the deletion mutation of Edelmann et al, such arguments have already been addressed in the response to part 1.3 of the Appeal Brief as detailed above.

Appellants argue (part 2.2 of the Appeal Brief) that there is no reasonable expectation of success for combining the methods of Edelmann et al and Doll et al to arrive at the method as claimed in claim 25. The arguments indicate that Edelmann et al and Doll et al does not provide demonstrate how to detect multiple types of mutations (deletion mutations and point mutations) on multiple amplicons in real time. As stated in the rejection, and discussed previously in this Examiner's Answer, Doll et al is relied upon for its teaching of the detection of specific nucleotide content in a real-time PCR format comprising primer-based amplification and hybridization-based detection using

probes. With specific regard to the argument concerning the detection of multiple mutations, Doll et al clearly teaches the simultaneous use of multiple different primers to detect multiple different nucleotide sequences (Table 2 and Fig. 2 of Doll et al). Edelmann et al provides teachings of the particular nucleotide sequences detected in a screen from Mucolipidosis IV-related mutations, and specifically includes teaches of multiplexed primer-based amplification (p.1024, left col., lns.23-36 of Edelmann et al) as well as hybridization-based detection of the resulting multiplex PCR products (p.1024, right col., lns.11-14) using probe hybridization to particular nucleotide sequences (p.1024, right col., lns.15-25). There is a reasonable expectation of success in the combination of the teachings of Doll et al and Edelmann et al because the references teach methods for the detection of specific nucleotide content using very similar techniques of primer-based sequence amplification and probe-based sequence detection by hybridization. There is a reasonable expectation of success in the combination of the teachings of Doll et al and Edelmann et al to arrive at the claimed methods as Edelmann et al clearly teaches the simultaneous multiplex amplification of different amplicons for detection of specific nucleotide sequences by hybridization, and Doll et al clearly teaches the simultaneous multiplex real-time detection of distinct nucleotide sequences using different probes.

Appellants argue (part 3.1 of the Appeal Brief) that Edelmann et al in view of Doll et al, GenBank AF287270, and Buck et al, cited in the rejection of claims 20-22, 26, 27, and 29-31, does not teach the specific primers and probes recited in the rejected claims. Appellants argue that claims 20, 21, 29 and 30 require the use of

oligonucleotide primers of SEQ ID NOs: 3 and 4 for the amplification of the deletion mutation of the MCOLN1 gene. However, this interpretation of the claims is not appropriate. For example, claims 20 and 29 require that 'the first oligonucleotide primer comprises a sequence that consists essentially of SEQ ID NO: 3'. As such, the breadth of claims 20 and 29 is such that the claim is drawn to a method requiring a primer that comprises (i.e. may contain any other unrecited sequence elements, as per MPEP 2111.03) SEQ ID NO: 3, not a primer that consists of (i.e. is limited only to the sequence presented) SEQ ID NO: 3. Furthermore, claims 20 and 29 have no limitations requiring the use of SEQ ID NO: 4 in the amplification of the deletion mutation of the MCOLN1 gene. As such, a characterization of the claims, more properly presenting the breadth of the claims than that provided by Appellants at the beginning of part 3.1 of the Appeal Brief, is that claims 20 and 29 require the use of an oligonucleotide primer comprising SEQ ID NO: 3 for the amplification of the deletion mutation of the MCOLN1 gene; claims 21 and 30 require the use of an oligonucleotide primer comprising SEQ ID NO: 4 for the amplification of the deletion mutation of the MCOLN1 gene; claims 22 and 31 require the use of an oligonucleotide probe comprising SEQ ID NO: 7 for the detection of the deletion mutation of the MCOLN1 gene; claim 26 requires the use of an oligonucleotide primer comprising SEQ ID NO: 1 for the amplification of the point mutation of the MCOLN1 gene; and claim 27 requires the use of an oligonucleotide primer comprising SEQ ID NO: 2 for the amplification of the point mutation of the MCOLN1 gene. None of the rejected claims recite specific limitations regarding the sequence comprising any more than any single specific primer

or probe; for example, while claim 31 requires that the 'second probe' in the method of claim 25 comprises SEQ ID NO: 7, claim 31 has no specific sequence limitations of the first, second, third or fourth primers required of the claim, or the first probe of the claim.

Appellants argue (part 3.1 of the Appeal Brief) that the combination of the teachings of Buck et al and GenBank AF287270 do not render obvious the broadly claimed primers and probes required of rejected claims 20-22, 26, 27, and 29-31. Appellants point out as an initial matter that with respect to claims 23 and 31 which relate to the use of the oligonucleotide probe of SEQ ID NO: 7, the Examiner has failed to provide any reasons why the use of this probe is obvious. The Examiner points out that claim 23 does not require the use of a probe of SEQ ID NO: 7, but claim 22 requires a probe comprising SEQ ID NO: 7. Regarding the rejection of claims 22 and 31, as set forth in the rejection, Edelmann et al teaches a primer suitable for the specific detection of the presence of the deletion mutation and the nature of the deletion mutation, GenBank AF287270 teaches the location of the sequence required for any probe comprising SEQ ID NO: 7, and Buck teaches the equivalence of primers. As such, given the breadth of the claims, where the claims require only that the probe comprises the sequence as set forth in SEQ ID NO: 7 (i.e. may contain any other unrecited sequence elements, such as the sequence of the probe specifically disclosed in Edelmann et al), the probe required in the claim is obvious.

Appellants argue (part 3.1 of the Appeal Brief) that Buck et al teaches the equivalency of sequencing primers, and that in contrast to sequencing primers, PCR primers are used in a reaction that creates a full copy of the target DNA in which the

primers are used in pairs to define the boundaries of the target DNA. The Examiner maintains that the teaching of Buck et al is directly related to the limitations of the rejected claims, and that Appellants interpretation of the teachings of Buck et al is too narrow. The analyses of Buck et al demonstrate the effective use of many different primers in a sequencing assay requiring site specific hybridization of the primer followed by polymerase-based extension of the primer, where the same elements are required in the real-time PCR assay of the instant invention. Thus the characteristics of the methods of Buck et al (i.e. primer-extension-based sequencing) and the instantly climaed methods (PCR-based analysis) are similar, where for example a sequencing primer is making a copy of the portion of the template molecule that is analyzed. The characterisitce of PCR primers of defining the boundaries of the target DNA is not essential to the design of the primer in the PCR-based assay of the instant claims versus the sequencing assay of Buck et al.

Appellants further argue, as provided in the Declaration of Dr. Sun, that the presently claimed invention requires the use of primers and hybridization probes in a complex real-time format, that the probes and primers must be capable of working together, and that there is no expectation that any set of PCR primers combined with any hybridization probe will be successful in a real time amplification assay. However, while Appellants' Declaration provides this statement, the Declaration provides no factual or experimental evidence suggesting that the primers of Edelmann et al, or the primers rendered obvious in light of the teachings of Edelmann et al in view of GenBank AF287270 and Buck et al, would not be expected to work in a real-time PCR assay as

taught by Doll et al and required by the instantly claimed methods. Furthermore, such arguments are not consistent with the broad scope of the primers and probes of the claimed methods. The breadth of the primers and probes required of claim 19 is evident in, for example, the limitations of the 'first oligonucleotide primer' (part a-i of claim 19) where the primer comprises a sequence complementary to a 15-30 bp segment of DNA between positions 100-500 of the MCOLN1 gene. As such, the first oligonucleotide primer minimally requires any sequence (which can be as little as two contiguous base pairs) that is complementary to any portion of a 15-30 bp segment (where the claim does not require a sequence complementary to the entire 15-30 bp segment; e.g. the sequence 5'-TT-3' is complementary to the 15 base DNA segment 5'-ACCGTATGCAAGCTC-3' because 5'-TT-3' is complementary to the positions 10-11 of the DNA segment) within positions 100-500 of the MCOLN1 gene. Claim 19 further requires another primer and a probe, each with equal breadth. Dependent claim 20 limits the sequence of the 'first oligonucleotide primer' of claim 19 only in that the primer comprises the sequence of SEQ ID NO: 3, thus the first primer has the sequence of SEQ ID NO: 3 and may contain any amount of any other unrecited sequence elements; within claim 20, the second oligonucleotide primer and probe retain the breadth of claim 19. As such Appellants arguments drawn to the strict requirements of primers and probes in order for there to be some expectation of success in a real-time format is not consistent with the breadth of the claims. Furthermore the Examiner maintains that in light of the analyses of Buck et al regarding the effectiveness of different primers in assays requiring primer hybridization and polymerase-based extension, the broadly

claimed primers and probes of the instantly claimed methods are obvious in view of the teachings of Edelmann et al, Doll et al, and GenBank AF287270.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Stephen Kapushoc

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